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COMPLETE SPECIFICATION

"ANTHELMINTIC COMPOSITION AND THE USE THEREOF"

~~I~~,WE SANKYO COMPANY LIMITED, 1-6,3-chome, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan, a Japanese company

hereby declare the invention, for which ~~I~~/we pray that a patent may be granted to ~~me~~/us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

(followed by page 1A.)

ANTHELMINTIC COMPOSITION AND THE USE THEREOF

The present invention relates to an anthelmintic composition comprising a mixture of a macrolide antibiotic selected from those of the B-41, C-076 and 22,23-dihydro C-076 series (all of which are known to have anthelmintic activity) with certain other known anthelmintic agents, whereby the anthelmintic activity of the composition is synergistically enhanced.

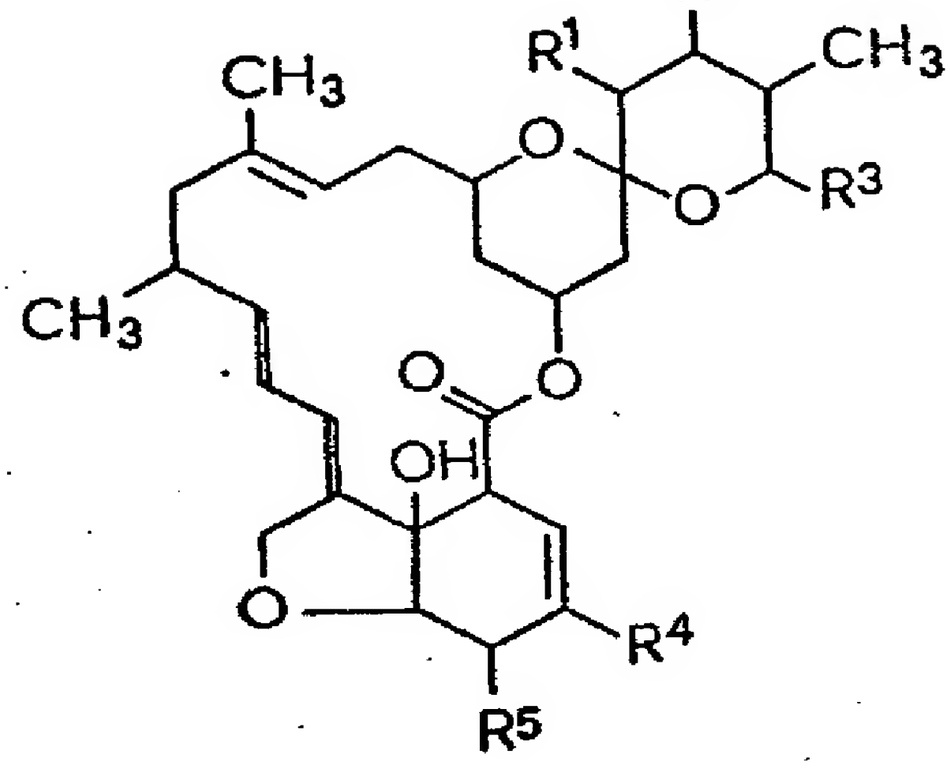
The compounds referred to herein as "B-41 series antibiotics", "C-076 series antibiotics" and "22,23-dihydro C-076 series antibiotics" are a group of macrolide antibiotics which, despite their different nomenclatures (arising from their different methods of production by various microorganisms), have very closely related molecular structures and activities.

The B-41 series antibiotics were originally isolated from a culture broth of Streptomyces B-41-146 strain (deposited with the Fermentation Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Japan, whence it is available under the Accession No. 1438).

Since the original discovery of the B-41 series

compounds, described in British Patent Specification No. 1,390,336, wherein nine compounds were characterized, a number of other compounds from the same series have been isolated from a culture broth of the same micro-organism. As disclosed in this British Patent Specification, these compounds may be prepared by cultivating a microorganism of the genus Streptomyces, preferably Streptomyces B-41-146 strain, in a suitable culture medium for a period of from 5 to 10 days at about 28°C under aerobic conditions, after which the culture broth is filtered through diatomaceous earth, the cake obtained is extracted with methanol and then with hexane to give an oily substance and finally the substance is fractionated by column chromatography through silica gel.

The B-41 series compounds thus include compounds having the following formulae (I) or (II), in which the groups represented by R^1 - R^6 are as defined in Tables 1 and 2.



(I)

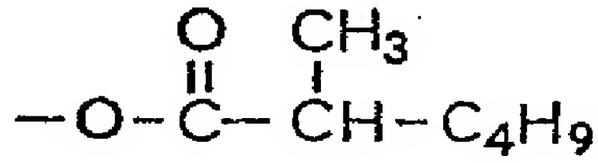
Table 1

B-41	R^1	R^2	R^3	R^4	R^5
α_1 (A_3)	H	H	CH_3	CH_3	OH
α_2 (B_2)	H	H	CH_3	CH_3	OCH_3
α_3 (A_4)	H	H	C_2H_5	CH_3	OH
α_4 (B_3)	H	H	C_2H_5	CH_3	OCH_3
(D)	H	H	i-C_3H_7	CH_3	OH
(G)	H	H	i-C_3H_7	CH_3	OCH_3
α_5 (A_2)	OH	MH	CH_3	CH_3	OH
α_6 (B_1)	OH	MH	CH_3	CH_3	OCH_3
α_7	OH	MH	C_2H_5	CH_3	OH
α_8	OH	MH	C_2H_5	CH_3	OCH_3
α_9 (C_1)	H	H	CH_3	PC	OH
α_{10} (C_2)	H	H	C_2H_5	PC	OH
(F)	H	H	i-C_3H_7	PC	OH

In this Table, the following abbreviations are used:

$i\text{-}C_3H_7$: means an isopropyl group,

MH: means a 2-methylhexanoyloxy group of formula



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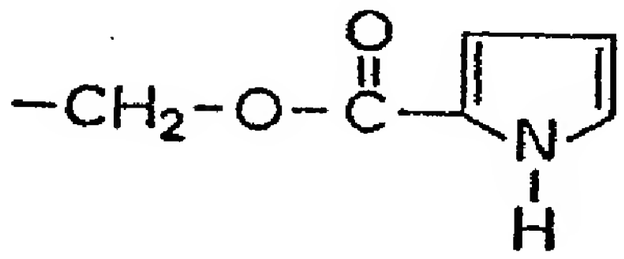
and

PC: means a 2-pyrrolylcarbonyloxymethyl group of formula



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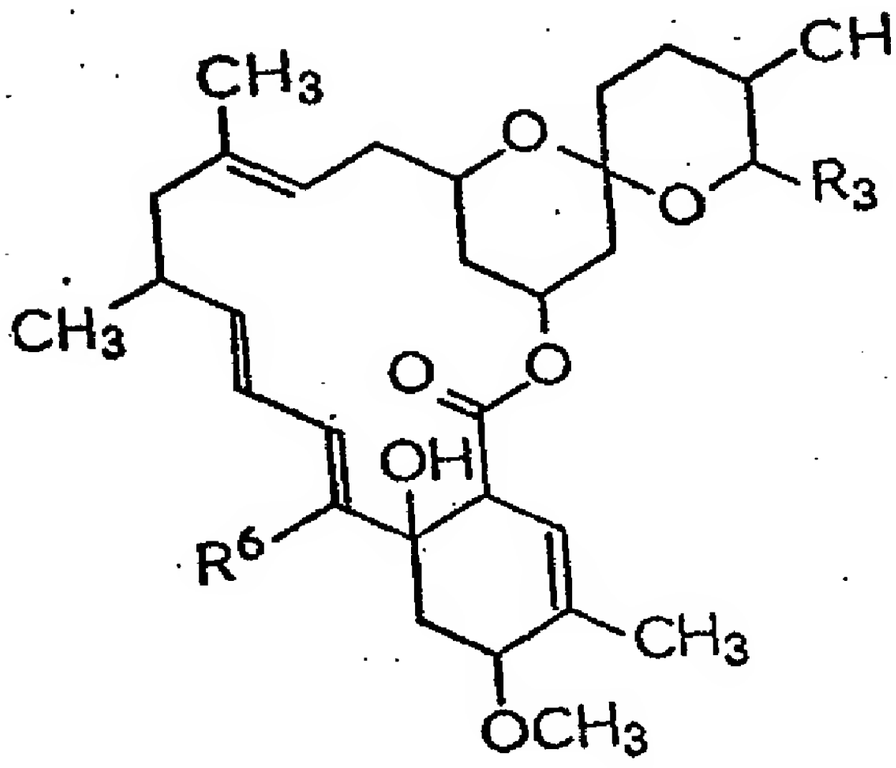


(II)

Table 2

B-41	R^3	R^6
β_1 (A_1)	CH_3	CH_2OH
β_2 (A_5)	C_2H_5	CH_2OH
(E)	$i\text{-}C_3H_7$	CH_2OH

Of the compounds shown above, those identified as A_1, A_2, A_3, A_4, A_5, B_1, B_2, B_3, C_1 and C_2 are described in British Patent Specification No. 1,390,336. Those compounds identified by α or β are described in The Journal of Antibiotics, 29(3), 76-14 to 76-16 and 29(6), 76-35 to 76-42 and the use of these compounds as anthelmintic agents is described in United States Patent Specification No:4144352. Compound B-41D is described in New Zealand Patent Specification No. 194742.

All of these compounds were obtained from a culture broth of the microorganism Streptomyces strain B-41-146 in the form of an amorphous powder. The properties of Compounds B-41D, B-41E, B-41F and B-41G are given below.

Compound B-41D

Molecular weight: 556

Ultraviolet Absorption Spectrum: 237mμ, 243mμ.

Infrared Absorption Spectrum: 3450, 1710 cm^{-1}.

Nuclear Magnetic Resonance Spectrum δ ppm:

1.52 (singlet, 14-CH_3);

1.86 (broad singlet, 4-CH_3);

3.94 (doublet, J=6.2 Hz, 6-H);

4.63 (singlet, 26-CH_2);

4.91 (broad triplet, J=8 Hz, 15-H).

Thin layer chromatography, R_f value = 0.4.

Compound B-41E

Molecular Weight: 572

Ultraviolet Absorption Spectrum : 241 mμ.

Infrared Absorption Spectrum : 3475, 1710 cm^{-1}.

Nuclear Magnetic Resonance Spectrum δ ppm:

1.59 (singlet, 14-CH_3);

1.81 (broad singlet, 4-CH_3);

3.06 (singlet, 5-OCH_3);

4.12 (doubled doublet, J = 4.5 and 12 Hz, 26-CH_2);

4.30 (doubled doublet, J = 6 and 12 Hz, 26-CH_2);

4.87 (broad triplet, J = 7 Hz, 15-CH=);

6.23 (doubled doublet, J = 11 and 12 Hz, 10-CH=);

6.43 (doublet, J = 11 Hz, 9-CH=).

Thin layer chromatography, R_f value : 0.61.

Compound B-41F

Molecular Weight: 665

Ultraviolet Absorption Spectrum : 245 mμ, 253 mμ.

Infrared Absorption Spectrum : 3320, 1730, 1710 cm^{-1}.

Nuclear Magnetic Resonance Spectrum δ ppm:

1.48 (singlet, 4-CH_3);

3.91 (doublet, J = 6 Hz, 6-H);

4.60 (singlet, 26-CH_2);

6.1 - 6.3 (1H, multiplet);

6.8 - 7.0 (2H, multiplet).

Thin layer chromatography, R_f value : 0.27.

Compound B-416

Molecular Weight: 570

Ultraviolet Absorption Spectrum : 237 mμ, 244 mμ.

Infrared Absorption Spectrum : 3475, 1715 cm^{-1}.

Nuclear Magnetic Resonance Spectrum δ ppm:

1.50 (singlet, 14-CH_3);

1.79 (broad singlet, 4-CH_3);

3.44 (singlet, 5-OCH_3);

4.59 (singlet, 26-CH_2);

4.89 (broad triplet, J = 8 Hz, 15-H).

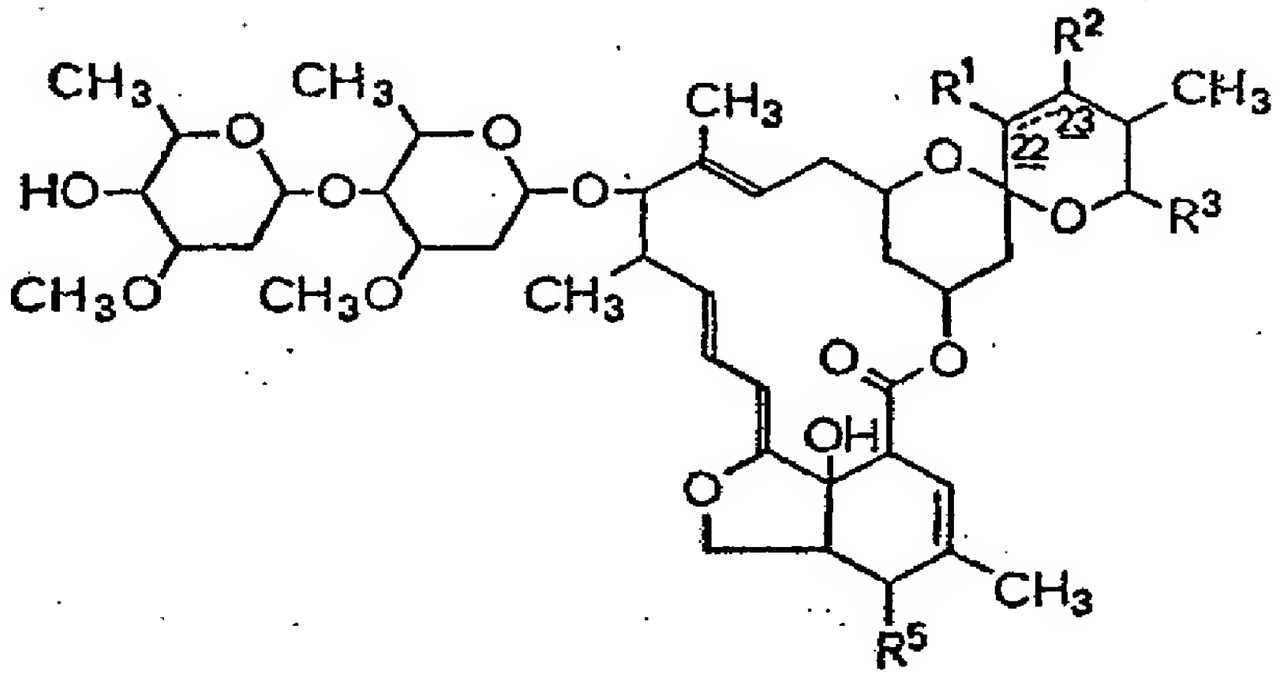
Thin layer chromatography, R_f value : 0.86.

In the above, the infrared absorption spectra were measured in a Nujol - trade mark - mull, the nuclear

magnetic resonance spectra were measured in $CDCl_3$ at a frequency of 100 MHz and the thin layer chromatography tests were carried out on Kieselgel 60 F_{254}, using a 18 : 42 by volume mixture of dioxan and carbon tetrachloride as the developing solvent.

The C-076 series compounds may be obtained from a C-076 producing strain of Streptomyces avermitilis (such as that deposited under the Accession No. NRRL-8165 at the Agricultural Research Service, Northern Regional Research Laboratory, Peoria, Illinois, U.S.A.). The use of these compounds as anthelmintic agents is described in Antimicrobial Agents and Chemotherapy 15, (3), 361-367 (1979). The 22,23-dihydro C-076 compounds and their preparation are described in European Patent Publication No. 1689.

The C-076 series and 22,23-dihydro C-076 series compounds include those represented by formula (III):



(III)

R^1 - R^5 are defined in the following Table 3 and the dotted line between the 22- and 23- positions represents either a single bond or a double bond. Where the dotted line represents a double bond, there are no substituents at the positions indicated by R^1 and R^2.

Table 3

C-076	R^1	R^2	R^3	R^5
A_{1a}	double bond		sec-C_4H_9	OCH_3
A_{1b}	double bond		i-C_3H_7	OCH_3
A_{2a}	H	OH	sec-C_4H_9	OCH_3
A_{2b}	H	OH	i-C_3H_7	OCH_3
B_{1a}	double bond		sec-C_4H_9	OH
B_{1b}	double bond		i-C_3H_7	OH
B_{2a}	H	OH	sec-C_4H_9	OH
B_{2b}	H	OH	i-C_3H_7	OH
Dihydro A_{1a}	H	H	sec-C_4H_9	OCH_3
Dihydro A_{1b}	H	H	i-C_3H_7	OCH_3
Dihydro B_{1a}	H	H	sec-C_4H_9	OH
Dihydro B_{1b}	H	H	i-C_3H_7	OH

Various benzimidazole compounds (for example Albendazole), salicylamide compounds (e.g. Niclosamide) and isoquinoline compounds (e.g. Praziquantel) are also known to have anthelmintic activity.

However, even the most valuable of therapeutic compounds is rarely free from side effects and, whilst these may not normally be serious, there is, naturally, a desire to reduce them. Clearly, if the anthelmintic activity of the known compounds could be increased without correspondingly increasing the intensity of the side effects, this would be a valuable contribution to the art.

We have now surprisingly discovered that the joint use of one or more of the B-41 series antibiotics, the C-076 series antibiotics or the 22,23-dihydro C-076 series antibiotics with one or more other anthelmintic agents selected from benzimidazole, salicylamide and isoquinoline compounds substantially enhances anthelmintic activity synergistically, without a corresponding increase in the intensity of side effects. As a result, it is possible to reduce substantially the dose of the anthelmintic agent and thus reduce side effects, such as intoxication.

Accordingly, in one aspect, the invention provides a composition comprising:

(a) one or more anthelmintic agents selected from the B-41 series antibiotics, the C-076 series antibiotics and the 22,23-dihydro C-076 series antibiotics; and

(b) one or more other anthelmintic agents selected from benzimidazole, salicylamide and isoquinoline compounds.

Examples of suitable benzimidazole series anthelmintic agents which may be used in the composition of the present invention include, for example:

2-(Methoxycarbonylamino)benzimidazole;

5-Butyl-2-(methoxycarbonylamino)benzimidazole;

5-Propoxy-2-(methoxycarbonylamino)benzimidazole;

5-Ethoxy-2-(ethoxycarbonylamino)benzimidazole;

5-Propylthio-2-(methoxycarbonylamino)benzimidazole;

5-Phenylthio-2-(methoxycarbonylamino)benzimidazole;

5-Phenylsulphinyl-2-(methoxycarbonylamino)benzimidazole;

5-(2,4-Dichlorophenoxy)-6-chloro-2-methylthiobenzimidazole;

6-Chloro-5-(2,3-dichlorophenoxy)-2-methylthiobenzimidazole;

2-(4-Thiazolyl)benzimidazole; and

5-Isopropoxycarbonylamino-2-(4-thiazolyl)benzimidazole.

Suitable salicylamide series anthelmintic agents which may be used in the composition of the present invention include, for example:

5-Chloro-N-(2-chloro-4-nitrophenyl)salicylamide;

3,5-Diiodo-N-(3-chloro-4-p-chlorophenoxyphenyl)-salicylamide;

3,5-Diiodo-N-[5-chloro-2-methyl-4-(α-cyano-4-chlorobenzyl)phenyl]salicylamide;

3,5,6-Trichloro-N-(3,5-dichloro-2-hydroxyphenyl)-salicylamide;

2-Acetoxy-3,5-diiodo-N-(p-chlorophenyl)benzamide; and

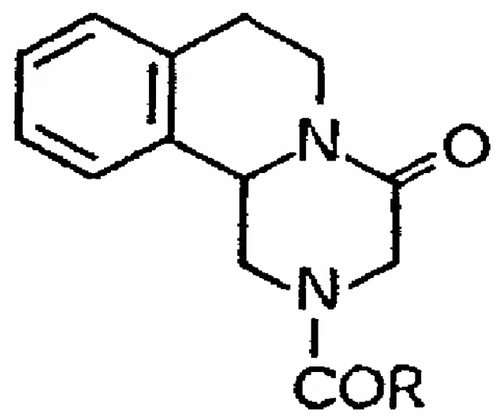
2-Acetoxy-3-bromo-5-chloro-N-(p-bromophenyl)-thiobenzamide.

Suitable isoquinoline series anthelmintic agents, which may be used in the composition of the present invention include, for example, L-isomers of:

2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline; and

2-Benzoyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

These isoquinoline compounds may be represented by the formula (IV):



(IV)

in which R represents a cyclohexyl or phenyl group, respectively.

Particularly preferred are combinations of B-41D, C-076 B_{1a}, C-076 B_{1b}, 22,23-dihydro C-076 B_{1a} or 22,23-dihydro C-076 B_{1b}, especially B-41D, with one or more of the abovementioned benzimidazole, salicylamide or isoquinoline series compounds.

The anthelmintic compositions of the invention are useful as parasiticides for the treatment of human beings and other animals. They are particularly useful for the treatment of diseases in livestock, poultry and pet animals (such as pigs, sheep, goats, cows, horses, dogs, cats and chickens) caused by the group of parasites known as the Nematoda, especially those of genera:

Haemonchus;

Trichostrongylus;

Ostertagia;

Nematodirus;

Cooperia;

Ascaris;

Bunostomum;

Oesophagostomum;

Chabertia;

Trichuris;

Strongylus;

Trichonema;

Dictyocaulus;

Capillaria;

Heterakis;

Toxocara;

Ascaridia;

Oxyuris;

Ancylostoma;

Uncinaria;

Toxascaris; and

Parascaris.

Some of the parasites of the genera Nematodirus, Cooperia and Oesophagostomum attack the intestines, whereas parasites of the genera Haemonchus and Ostertagia attack the stomach and parasites of the genus Dictyocaulus are found in the lungs. Parasites of the families Filariidae or Setariidae are found in the heart, the blood vessels and tissues and organs such as the subcutaneous tissues and lymphatic vessels.

The compositions of the invention may also be used for the treatment of diseases caused by, for example, the following Cestoidea:

Taenia saginata;

Hymenolepis diminuta;

Hymenolepis nana;

Moniezia benedeni;

Diphyllobothrium latum;

Diphyllobothrium erinacei;

Echinococcus glanulosus; and

Echinococcus multilocularis,

and caused by the following Trematoda:

Fasciola hepatica;

Fasciola gigantica;

Paragonimus westermanii;

Fasciolopsis buski;

Eurytrema pancreaticum;

Eurytrema coelomaticum;

Clonorchis sinensis;

Schistosoma japonicum;

Schistosoma haematobium; and

Schistosoma mansoni.

The anthelmintic compositions of the invention may be administered orally. One suitable oral formulation is as a drink, in which case the composition may be formulated as an aqueous solution, as a solution in another suitable non-toxic solvent or as a suspension or dispersion incorporating a suspension aid and a wetting agent (such as bentonite) or other constituents.

The composition of the invention may also be administered as a solid, suitably in unit dosage form, for example as a capsule, pill or tablet containing a predetermined amount of the active ingredients. These formulations can be prepared by homogeneously mixing the active ingredients with one or more other finely pulverized materials, generally diluents, filling agents, disintegrators and/or binding agents (e.g. starch, lactose, talc, magnesium stearate or vegetable gum). The weight and content of the active ingredients in such unit dosage forms may vary widely, depending upon the type of animal to be treated, the degree of infection, the kind of parasite and the body weight of the animal.

The anthelmintic compositions of the invention may also be administered to animals by uniformly dispersing them in their feed or they may be used as a top dressing or in the form of pellets.

The active ingredients may also be dissolved or dispersed in a liquid carrier and administered parenterally to animals by injection into the proventriculus, the muscles, the lungs or under the skin. For parenteral administration, the carrier used is preferably a vegetable oil, such as peanut oil or cottonseed oil.

Topical administration of the compositions of

the invention is also possible, in which case the active ingredients are preferably mixed with a suitable carrier (such as dimethyl sulphoxide or a hydrocarbon solvent). The resulting formulation can be directly applied to the outer skin of the animals, e.g. by spraying.

The optimum amount of the active ingredients of the composition of the invention desired to achieve best results will vary depending upon the kind of animal to be treated, the type of parasitic infection and the degree of infection. However, in general, we have found that good results are achieved by using, for oral administration, from 0.01 to 100 mg, preferably from 0.1 to 50 mg, of the B-41, C-076 or 22,23-dihydro C-076 series antibiotics and from 0.5 to 200 mg, preferably from 1 to 30 mg, of the benzimidazole, salicylamide or isoquinoline compound, per kg body weight.

The enhanced activities of the compositions of the invention are illustrated by the following Examples.

EXAMPLE 1

The test animals used in this Example were goats (two per test group) parasitized by Haemonchus contortus, Ostertagia ostertagi and Fasciola species.

Each goat was given a single gelatin capsule containing the amount of B-41D and/or Albendazole [i.e. 5-propylthio-2-(methoxycarbonylamino)benzimidazole] shown in Table 4. The number of eggs per gram of faeces (E.P.G.) before and after administration was determined. 14 days after administration, the goats were sacrificed and the number of living parasites was determined. These results are also shown in Table 4.

The names of the parasites are abbreviated in the Table as follows:

H.c = Haemonchus contortus

O.o = Ostertagia ostertagi

F.sp. = Fasciola species

Table 4

Anthelmintic efficacy in goats by single and joint use of B-41D with Albendazole against Haemonchus contortus, Ostertagia ostertagi and Fasciola sp.

Compound and amount (mg/kg)		E.P.G. of H.c and O.o before adminstr.	after administr. 7 days	14 days	E.P.G. of F.sp. before administr.	after administr. 14 days
B-41D	0.2	3200	0	0	450	990
		4400	0	0	880	620
B-41D	0.05	3400	0	100	1320	940
		2000	0	80	480	860
B-41D + Albendazole	0.05 + 2.5	4300	0	0	920	0
		600	0	0	810	0
B-41D + Albendazole	0.05 + 5	3800	0	0	1100	0
		2900	0	0	540	0
Albendazole	5	3300	0	0	760	20
		900	0	0	320	10
None		2100	4210	3600	1800	1980
		3700	3100	2800	1710	1220

Table 4 (continued)

Number of living parasites at autopsy			Reduction rate (%)		
H.c	O.o	F.sp.	H.c	O.o	F.sp.
0	0	21	100	100	32.0
0	0	13			
78	455	19	68.2	70.5	34.0
51	431	14			
0	0	0	100	100	100
0	0	0			
0	0	0	100	100	100
0	0	0			
0	0	8	100	100	72.0
0	0	6			
162	1022	27			
244	1982	23			

EXAMPLE 2

The animals used in this Example were dogs (two per test group) parasitized by Toxocara canis (T.c), Ancylostoma caninum (A.c) and Dipylidium caninum (D.c). Each dog was given a single gelatin capsule containing the prescribed amounts of B-41D and/or Niclosamide [i.e. 5-chloro-N-(2-chloro-4-nitrophenyl)salicylamide], as shown in Table 5. The E.P.G. and the number of parasites excreted before and after administration were determined. The dogs were sacrificed 7 days after administration and the number of living parasites was determined. It was confirmed that Dipylidium caninum excreted its segments in the faeces before administration of the drugs.

The results are shown in Table 5.

Table 5

Anthelmintic efficacy in dogs by singe and joint use of B-41D with Niclosamide against Toxocara canis, Ancylostoma caninum and Dipylidium caninum

Compound and amount (mg/kg)		E.P.G. before administr. T.c	A.c	E.P.G. after administr. (7 days) T.c	A.c	Number of excreted parasites (for 7 days) T.c	A.c
B-41D	0.1	13400	1400	0	0	24	13
		600	900	0	0	9	8
B-41D	0.025	2100	750	0	30	7	9
		8400	1100	0	100	12	11
B-41D + Niclosamide	0.025 + 75	2600	500	0	0	13	10
		600	450	0	0	4	16
B-41D + Niclosamide	0.025 + 150	1800	350	0	0	8	6
		1500	1450	0	0	9	23
Niclosamide	150	3200	2100	2600	1200	0	1
		4100	800	3100	450	0	0
None		2400	2300	1800	3400	0	0
		2100	850	3400	1600	0	0

Table 5 (continued)

Number of living parasites at autopsy			Reduction rate (%)		
T.c	A.c	D.c	T.c	A.c	D.c
0	0	16	100	100	23.2
0	0	27			
3	3	11	67.8	71.4	23.2
6	5	32			
0	0	0	100	100	100
0	0	0			
0	0	0	100	100	100
0	0	0			
6	14	8	13.0	31.0	73.2
14	6	7			
8	21	37			
15	8	19			

EXAMPLE 3

The test animals used in this Example were dogs (two per test group) parasitized by Trichuris vulpis (T.v) and Dipylidium caninum (D.c). Each dog was given a single gelatin capsule containing the prescribed amount of B-41D and/or Praziquantel (i.e. 1-2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2.1-a]isoquinoline). The E.P.G. and number of parasites before and after administration were determined. The dogs were sacrificed 7 days after administration and the number of living parasites was also determined. It was confirmed that Dipylidium caninum excreted its segments in the faeces before administration of the drugs.

The results are shown in Table 6.

Table 6

Anthelmintic efficacy in dogs by single and joint use of B-41D with Praziquantel against Trichuris vulpis and Dipylidium caninum

Compound and amount (mg/kg)		E.P.G. of T.v. before administr.	E.P.G. of T.v. after administr. (7 days)	Number of excreted parasites (for 7 days)
B-41D	0.1	800	0	68
		100	0	18
B-41D	0.05	1600	300	181
		900	200	88
B-41D + Praziquantel	0.05 + 2.5	300	0	0
		1400	0	0
B-41D + Praziquantel	0.05 + 5	500	0	0
		200	0	0
Praziquantel	5	700	300	0
		600	800	0
None		1100	600	0
		700	400	0

Table 6 (Continued)

Number of living parasites at autopsy		Reduction rate (%)	
T.v.	D.c.	T.v.	D.c.
0	17	100	16.6
0	28		
58	9	75.1	22.2
31	33		
0	0	100	100
0	0		
0	0	100	100
0	0		
142	6	-	77.7
263	6		
165	32		
97	22		

From the above results, it is apparent that B-41D, when used alone is ineffective against Trematoda (such as the liver fluke) but, when used together with Albendazole, the combination shows more activity than does Albendazole alone.

Niclosamide alone is ineffective against such Nematoda as Toxocara canis and Ancylostoma caninum, whilst B-41D alone is ineffective against Dipylidium caninum, but the combination of the two compounds shows more activity against all of these parasites than do the respective active compounds when used alone.

Praziquantel alone is ineffective against such Nematoda as Trichuris vulpis but, when it is used jointly with B-41D, the combination shows greater activity than B-41D against both Nematodae and Cestoidea.

Moreover, the compounds, when used jointly, are effective in much smaller doses than are the compounds when used alone, thus strongly suggesting the presence of synergism.

WHAT WE CLAIM IS:

1. An anthelmintic composition comprising a synergistic mixture of:

(a) one or more macrolide anthelmintic agents selected from B-41 series antibiotics, C-076 series antibiotics and 22,23-dihydro C-076 derivatives; and

(b) one or more anthelmintic agents selected from benzimidazole, salicylamide and isoquinoline compounds.

2. A composition as claimed in Claim 1, in which said macrolide anthelmintic agent (a) is B-41D.

3. A composition as claimed in Claim 1, in which the macrolide anthelmintic agent (a) is C-076 B_{1a}, C-076 B_{1b}, 22,23-dihydro C-076 B_{1a} or 22,23-dihydro C-076 B_{1b}.

4. A composition as claimed in any one of Claims 1 to 3, in which said anthelmintic agent (b) is one or more of the compounds:

2-(Methoxycarbonylamino)benzimidazole;

5-Butyl-2-(methoxycarbonylamino)benzimidazole;

5-Propoxy-2-(methoxycarbonylamino)benzimidazole;

5-Ethoxy-2-(ethoxycarbonylamino)benzimidazole;

5-Propylthio-2-(methoxycarbonylamino)benzimidazole;

5-Phenylthio-2-(methoxycarbonylamino)benzimidazole;

5-Phenylsulphinyl-2-(methoxycarbonylamino)benzimidazole;

5-(2,4-Dichlorophenoxy)-6-chloro-2-methylthiobenzimidazole;

6-Chloro-5-(2,3-dichlorophenoxy)-2-methylthiobenzimidazole;

2-(4-Thiazolyl)benzimidazole;

5-Isopropoxycarbonylamino-2-(4-thiazolyl)benzimidazole;

5-Chloro-N-(2-chloro-4-nitrophenyl)salicylamide;

3,5-Diiodo-N-(3-chloro-4-p-chlorophenoxyphenyl)-salicylamide;

3,5-Diiodo-N-[5-chloro-2-methyl-4-(α-cyano-4-chlorobenzyl)phenyl]salicylamide;

3,5,6-Trichloro-N-(3,5-dichloro-2-hydroxyphenyl)-salicylamide;

2-Acetoxy-3,5-diiodo-N-(p-chlorophenyl)benzamide;

2-Acetoxy-3-bromo-5-chloro-N-(p-bromophenyl)-thiobenzamide;

L-2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline; and

L-2-Benzoyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

5. A composition as claimed in Claim 1, comprising B-41D and 5-propylthio-2-(methoxycarbonylamino)benzimidazole.

6. A composition as claimed in Claim 1, comprising B-41D and 5-chloro-N-(2-chloro-4-nitrophenyl)salicylamide.

7. A composition as claimed in Claim 1, comprising B-41D and 1-2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

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END